Intensive Care Med (2012) 38:1573–1582
DOI 10.1007/s00134-012-2682-1

SPECIAL ARTICLE

The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material

Niall D. Ferguson
Eddy Fan
Luigi Camporota
Massimo Antonelli
Antonio Anzueto
Richard Beale
Laurent Brochard
Roy Brower
Andrés Esteban
Luciano Gattinoni
Andrew Rhodes
Arthur S. Slutsky
Jean-Louis Vincent
Gordon D. Rubenfeld
B. Taylor Thompson
V. Marco Ranieri

Received: 14 June 2012
Accepted: 27 July 2012
Published online: 25 August 2012

An initiative of the European Society of Intensive Care Medicine endorsed by the American Thoracic Society, the Society of Critical Care Medicine and the European Respiratory Society.

G. D. Rubenfeld, B. T. Thompson and V. M. Ranieri contributed equally to this work as co-chairs of the Task Force.

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-012-2682-1) contains supplementary material, which is available to authorized users.

N. D. Ferguson (✉)
Interdepartmental Division of Critical Care Medicine, and Department of Medicine, Division of Respirology, University Health Network and Mount Sinai Hospital, University of Toronto, 600 University Avenue, Suite 18-206, Toronto, ON M5G 1X5, Canada
e-mail: n.ferguson@utoronto.ca
Tel.: +1-416-5868449
Fax: +1-416-5865981

E. Fan
Interdepartmental Division of Critical Care Medicine, and Department of Medicine, University Health Network and Mount Sinai Hospital, University of Toronto, Toronto, Canada

L. Camporota · R. Beale
Division of Asthma, Allergy and Lung Biology, King's College London and Department of Adult Critical Care, Guy's and St Thomas' NHS Foundation Trust, King's Health Partners, London, UK

M. Antonelli
Dipartimento di Anestesia e Rianimazione, Universita Cattolica del Sacro Cuore, Rome, Italy

A. Anzueto
Pulmonary/Critical Care, University of Texas Health Sciences Center at San Antonio, and South Texas Veterans Health Care System, San Antonio, TX, USA

L. Brochard
Medical-Surgical Intensive Care Unit, Hopitaux Universitaires de Geneve, Geneva, Switzerland

R. Brower
Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, MD, USA

A. Esteban
Servicio de Cuidados Intensivos, Hospital Universitario de Getafe. CIBER de Enfermedades Respiratorias, Instituto Salud Carlos III, Madrid, Spain

L. Gattinoni
Istituto di Anestesiologia e Rianimazione, Universita degli Studi di Milano, Milan, Italy

A. Rhodes
Department of Intensive Care Medicine, St. George's Healthcare NHS Trust, London, UK

A. S. Slutsky
Keenan Research Center of the Li KaShing Knowledge Institute of St. Michael's Hospital; Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada

J.-L. Vincent
Department of Intensive Care, Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium

G. D. Rubenfeld
Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada

B. T. Thompson
Pulmonary/Critical Care Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

V. M. Ranieri
Department of Anesthesia and Intensive Care Medicine, University of Turin, Turin, Italy

Abstract *Purpose:* Our objective was to revise the definition of acute respiratory distress syndrome (ARDS) using a conceptual model

incorporating reliability and validity, and a novel iterative approach with formal evaluation of the definition. *Methods:* The European Society of Intensive Care Medicine identified three chairs with broad expertise in ARDS who selected the participants and created the agenda. After 2 days of consensus discussions a draft definition was developed, which then underwent empiric evaluation followed by consensus revision. *Results:* The Berlin Definition of ARDS maintains a link to prior definitions with diagnostic criteria of timing, chest imaging, origin of edema, and hypoxemia. Patients may have ARDS if the onset is within 1 week of a known clinical insult or new/worsening respiratory symptoms. For the bilateral opacities on chest radiograph criterion, a reference set of chest radiographs has been developed to enhance inter-observer reliability. The pulmonary artery wedge pressure criterion for hydrostatic edema was removed, and illustrative vignettes were created to guide judgments about the primary cause of respiratory failure. If no risk factor for ARDS is apparent, however, objective evaluation (e.g., echocardiography) is required to help rule out hydrostatic edema. A minimum level of positive end-expiratory pressure and mutually exclusive PaO_2/FiO_2 thresholds were chosen for the different levels of ARDS severity (mild, moderate, severe) to better categorize patients with different outcomes and potential responses to therapy. *Conclusions:* This panel addressed some of the limitations of the prior ARDS definition by incorporating current data, physiologic concepts, and clinical trials results to develop the Berlin definition, which should facilitate case recognition and better match treatment options to severity in both research trials and clinical practice.

Keywords Diagnosis · International cooperation · Prognosis · Respiration, artificial · Respiratory distress syndrome, adult · Risk factors

Abbreviations

ARDS	Acute respiratory distress syndrome
ECLS	Extracorporeal life support
FiO_2	Fraction of inspired oxygen
HFO	High frequency oscillation
PaO_2	Partial pressure of arterial oxygen
PEEP	Positive end-expiratory pressure

Introduction

The first definition of acute respiratory distress syndrome (ARDS) dates to Ashbaugh and colleagues in 1967 when they described 12 patients with severe acute respiratory failure [1]. These patients had severe hypoxemia that was refractory to supplemental oxygen, but which in some cases was responsive to the application of positive end-expiratory pressure (PEEP). Widespread pulmonary inflammation, edema, and hyaline membranes were observed on autopsy.

Over the next 25 years several definitions were proposed, but there was no single definition for ARDS that was widely accepted and used. In 1994, broad consensus was achieved when the American-European Consensus Conference (AECC) published a definition [2, 3]. This group defined ARDS as the acute onset of hypoxemia (the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen [PaO_2/FiO_2] $\leq$200 mmHg), with bilateral infiltrates on frontal chest X-ray, in the absence of left atrial hypertension. They also defined a new over-arching entity termed acute lung injury (ALI), which used the same variables but with a less stringent criterion for hypoxemia (PaO_2/FiO_2 $\leq$300 mmHg).

The AECC definition has been widely adopted by clinicians and researchers and has facilitated the acquisition of a great deal of data about ARDS in the ensuing two decades. Over this same time, however, a number of issues with the AECC definition have become apparent [4, 5]. Evaluating the definition as a whole, a modified AECC definition (applied retrospectively using the entire ICU length of stay and requiring four-quadrant air-space disease) was compared to a reference standard of diffuse alveolar damage seen on autopsy. Under these conditions the AECC definition performed reasonably well, with a sensitivity of 75 % and a specificity of 84 % [6]. However, when the AECC definition criteria were strictly applied (bilateral chest X-ray infiltrates) on a daily basis, the sensitivity remained reasonable at 84 %, but the specificity was significantly lower at only 51 % [7]. Moreover, ALI, as defined using the AECC criteria, is under-recognized by clinicians, particularly the subgroup of patients with milder hypoxemia (i.e., with PaO_2/FiO_2 201–300) [7–9].

The AECC definition requires that onset of respiratory failure be acute, but does not explicitly define the specific timeframe (e.g., hours, days, or weeks). The hypoxemia criterion has generated concerns because PaO_2/FiO_2 may vary with FiO_2, and also in response to other ventilator settings, particularly PEEP [10–15]. The chest X-ray criterion has only moderate inter-observer reliability even when applied by experts, although this can be improved through use of a training set of radiographs [16, 17]. Finally, although the AECC definition includes a pulmonary artery wedge pressure (PAWP) $\leq$18 mm Hg (when measured), patients with hallmark findings of ARDS often have an elevated PAWP because of elevated pleural pressures and/or vigorous fluid resuscitation [18, 19].

For these reasons and because all definitions should be reviewed and adjusted periodically to reflect new information and experience, we convened a consensus panel to address the limitations of the previous AECC definition and propose revisions. The methodology and the empirical evaluation of the Berlin definition have been published previously [22]; the current publication provides an expanded discussion of the rationale underlying the development of the Berlin definition, and provides further supplementary material (e.g., examples of typical chest X-rays from patients with ARDS) to facilitate its application.

Methods

As described previously [22], the panel revised the definition of ARDS for use in clinical practice and clinical research, using a conceptual model incorporating reliability, validity and a novel iterative approach that included a formal evaluation of the definition using large cohorts of patients with the syndrome (as originally defined using the AECC definition). The Task Force was initiated by the European Society of intensive care medicine (ESICM), which supported the process with an unrestricted grant and all necessary logistics. This grant covered the costs of the face-to-face meeting in Berlin and also a number of subsequent teleconferences. There was no support received from industry for any part of the process.

The ESICM identified three chairs with expertise in ARDS, clinical epidemiology, physiology, and clinical trials (Ranieri, Rubenfeld, and Thompson), who together selected the participants and created the agenda. Panelists (listed in the Appendix) were selected based on their recognized expertise in the field of ARDS, and to ensure intellectual diversity. Specifically, the chairs tried to achieve a balance of opinions by clinicians, trialists, epidemiologists, physiologists, and basic scientists. The chairs also included two junior members with an interest in ARDS.

All modifications to the ARDS definition were based on the principle that syndrome definitions must fulfill three criteria: feasibility, reliability and validity [20]. Feasible definitions should rely on diagnostic tests and/or clinical data that are routinely used by intensivists and can be performed in a short enough time frame to facilitate clinical trial enrolment. Since it is essential for researchers to identify patients with similar characteristics across studies, and for clinicians to apply the results of research at the bedside, syndrome definitions must be reliable as measured by inter-observer agreement. The most common technique to establish the validity of diagnostic criteria requires a gold standard, which is not available in ARDS. However, many syndromes in medicine are defined without a reference standard including depression, sepsis, and community-acquired pneumonia. Various indirect approaches exist to evaluate validity (e.g., face, construct, predictive, and concurrent validity) for syndromes that do not have reference standards (Table 1). In addition to feasibility and reliability, we emphasized face validity (the "conceptual model" of how clinicians recognize the syndrome) and predictive validity (the ability of the syndrome definition to predict outcome and/or response to therapy). Finally, the panel felt that any revision of the definition should be compatible with prior definitions to facilitate interpretation of older studies.

Each presenter was asked to evaluate potential defining criteria using a framework focusing on reliability, feasibility, and validity. We used an informal consensus

Table 1 Glossary of terms and their application in the Berlin definition

	Definition	Addressed in the Berlin definition With
Feasibility	Definition can be applied widely in actual practice	Maintenance of similar feasible criteria as AECC Removal of pulmonary artery catheter criteria
Reliability	Observers agree on case identification	Chest radiograph examples Inclusion of minimal PEEP levels Case vignettes to assess hydrostatic edema exclusion
Criterion validity	Definition agrees with reference standard	N/A
Predictive validity	Definition is able to stratify patients by prognosis or response to therapy	Creation of categories of ARDS severity
Face validity	Definition identifies patients who look like patients with the syndrome	Development of conceptual model of ARDS Chest radiograph examples Removal of clinical evidence of left atrial hypertension exclusion
Content validity	Definition captures all relevant aspects of the syndrome	Concordance with previous AECC definition Expert consensus

AECC American-European Consensus Conference, *ARDS* acute respiratory distress syndrome, *CT* computed tomography, FiO_2 fraction of inspired oxygen, SpO_2 oxyhemoglobin saturation by pulse oximetry

technique involving whole group discussions moderated by one of the chairs, conducted in-person and by teleconference. Consensus was demonstrated by unanimous consent around presented options. When issues were contentious, individual yes/no votes were counted to ensure that all panelists had an opportunity to voice their opinion.

After 2 days of in-person discussions (September 30–October 1, 2011) in Berlin, Germany a draft definition was proposed [21]. This draft definition was then evaluated using existing ARDS databases to determine characteristics of patients in each category of ARDS and examine predictive validity for mortality. Finally, the panel reconvened by multiple teleconferences in February 2012 to conduct further discussions and produce the final Berlin Definition of ARDS [22]. Prior to submission for publication the consensus definition underwent a process of independent peer review and subsequent endorsement by each of the ESICM, the American Thoracic Society, and the Society of Critical Care Medicine.

The ARDS conceptual model

Face validity derives from an understanding of how clinicians recognize patients with the syndrome, therefore, considerable discussion focused on developing a conceptual model of ARDS. The panel agreed that ARDS is a type of acute diffuse lung injury associated with a predisposing risk factor, characterized by inflammation leading to increased pulmonary vascular permeability and loss of aerated lung tissue. The hallmarks of the clinical syndrome are hypoxemia and bilateral radiographic opacities [23] (using standard chest X-ray or computed tomography [CT] scan), associated with several physiological derangements including: increased pulmonary venous admixture, increased physiological dead space, and decreased respiratory system compliance. The morphological hallmarks in the acute phase are lung edema, inflammation, hyaline membranes, and alveolar hemorrhage (i.e., diffuse alveolar damage) [24].

There are many common etiologic risk factors for ARDS, which the AECC definition classified into direct and indirect lung injury categories. Although some experimental and clinical studies show modest overall differences in the inflammatory responses and radiographic patterns as well as physiologic responses to ventilatory treatment, the direct and indirect categories overlap to such a large degree that the committee decided not to include direct and indirect ARDS as distinct entities in the Berlin definition (Table 2). Identification of the risk factor leading to ARDS in an individual patient, regardless of its direct or indirect nature, rather serves to guide therapy for the underlying disease leading to ARDS.

Table 2 Common risk factors for ARDS (adapted with permission [22])

Risk factor
Pneumonia
Non-pulmonary sepsis
Aspiration of gastric contents
Major trauma
Pulmonary contusion
Pancreatitis
Inhalational injury
Severe burns
Non-cardiogenic shock
Drug overdose
Multiple transfusions or transfusion-associated acute lung injury (TRALI)
Pulmonary vasculitis
Drowning

The Berlin ARDS definition

The resultant "Berlin Definition" has been published previously and is outlined in Table 3 [22]. Three mutually exclusive categories of mild, moderate, and severe ARDS were created to provide better separation of prognosis and treatment selection. The rationale, controversies, and recommendations for each diagnostic criterion are discussed in the following sections.

The original AECC definition stated that the onset of ARDS was acute, to exclude chronic pulmonary conditions that can cause hypoxemic respiratory failure, however, it did not state an explicit time frame. Observational data suggest that the majority of patients with ARDS are identified within 72 h of the recognition of the underlying risk factor, with nearly all patients identified within 7 days [25, 26]. The panel therefore defined "acute onset" as ARDS developing within 1 week of a known clinical insult or new/worsening respiratory symptoms.

The AECC definition required bilateral infiltrates consistent with pulmonary edema on frontal chest radiograph, but there is poor inter-observer reliability in interpreting chest radiographs using this definition among intensivists and radiologists [16, 17]. To help address this issue the panel attempted to make the chest radiograph criterion more explicit specifying that it should include bilateral opacities consistent with pulmonary edema that are not fully explained by effusions, lobar/lung collapse, or nodules/masses on chest radiograph as a defining criterion for ARDS, and also recognized that opacities seen on CT scan could be substituted if available. The CT scan abnormalities were not included in the definition as a core part of the definition because they were not considered feasible at the current time due to concerns regarding safety, cost, and lack of widespread availability. In addition, to enhance inter-observer reliability, we have included a set of chest radiographs judged by the panel to

Table 3 The Berlin definition of ARDS (with permission from [22])

	Acute respiratory distress syndrome		
Timing	Within 1 week of a known clinical insult or new/worsening respiratory symptoms		
Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules		
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload; Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present		
	Mild	Moderate	Severe
Oxygenation[b]	$200 < PaO_2/FiO_2 \leq 300$ with PEEP or CPAP ≥ 5 cmH_2O[c]	$100 < PaO_2/FiO_2 \leq 200$ with PEEP ≥ 5 cmH_2O	$PaO_2/FiO2 \leq 100$ with PEEP ≥ 5 cmH_2O

ARDS acute respiratory distress syndrome, *PaO_2* partial pressure of arterial oxygen, *FiO_2* fraction of inspired oxygen, *PEEP* positive end-expiratory pressure, *CPAP* continuous positive airway pressure, *N/A* not applicable

[a] Chest X-ray or CT scan

[b] If altitude higher than 1000 m, correction factor should be made as follows: $PaO_2/FiO_2 \times$ (barometric pressure/760)

[c] This may be delivered non-invasively in the mild ARDS group

be illustrative of the spectrum of images that are consistent, inconsistent, or equivocal for the diagnosis of ARDS (see Online Supplement for images and accompanying commentary). The committee considered a requirement for more extensive opacities (i.e., at least three quadrants) to define severe ARDS; however, this did not improve predictive validity for mortality and was dropped after further consensus discussion [22].

As with the AECC definition, the panel recognized that hydrostatic edema (i.e., cardiac failure or fluid overload) is one of the most common alternative diagnoses in patients presenting with ARDS. However, given the declining use of pulmonary artery catheters worldwide and the recognition that hydrostatic edema and ARDS may coexist [18, 19], the pulmonary artery wedge pressure (PAWP) criterion was removed. The panel therefore decided that patients whose respiratory failure is not fully explained by cardiac failure or fluid overload as judged by the treating physician using all available data may qualify as having ARDS. Nevertheless, if no known etiologic risk factor for ARDS is apparent (Table 2), objective evaluation of cardiac function (e.g., echocardiography or cardiac output measurement) is required to help rule out hydrostatic edema secondary to heart failure. In order to improve reliability and clarity in judging this criterion, the panel also developed a number of clinical vignettes illustrating cases that would and would not qualify as ARDS based on ruling out hydrostatic edema (Online Supplement).

The AECC definition classified ARDS by PaO_2/FiO_2 ratio regardless of the level of PEEP [2]. Since PEEP can affect the reliability and specificity of PaO_2/FiO_2, to classify the severity of ARDS [10, 13], a minimum level of 5 cm H_2O PEEP (or non-invasive CPAP for Mild ARDS) has been included in the updated definition. The panel had originally proposed a requirement of PEEP $\geq$10 cm H_2O as a criterion for the severe ARDS group, but this was subsequently dropped as it did not improve predictive validity for mortality within the group of patients with $PaO_2/FiO_2 \leq 100$ [22].

Recent data suggest that for a given PaO_2/FiO_2 ratio, higher FiO_2 is associated with a higher mortality [15]; however, since clinicians normally titrate FiO_2 to maintain a PaO_2 between 60–80 mm Hg, most patients with a $PaO_2/FiO_2 \leq 100$ mm Hg already have a FiO_2 of 0.7 or higher. Therefore, to avoid additional complexity that may have decreased feasibility; the committee did not add a minimum FiO_2 requirement to the definition.

Some physicians rely on oxyhemoglobin saturation by pulse oximetry (SpO_2) instead of arterial blood gas analysis to monitor arterial oxygenation, especially in patients with less severe ARDS. The SpO_2/FiO_2 ratio correlates with the PaO_2/FiO_2 ratio [27], so feasibility of the definition could be enhanced by the use of SpO_2 in place of PaO_2. However, in some patients SpO_2 is not concordant with PaO_2 [28]. In particular, with SpO_2/FiO_2 patients receiving FiO_2 of 1.0 and with SpO_2 of 100 % could be classified as Severe ARDS, regardless of their PaO_2, and therefore the SpO_2/FiO_2 ratio may misclassify patients. Therefore, the committee did not include SpO_2/FiO_2 as an alternative to PaO_2/FiO_2 in the revised definition.

The term acute lung injury (ALI) (i.e., all patients with $PaO_2/FiO_2 \leq 300$) was removed from the ARDS definition, due to the perception that many clinicians and researchers viewed ALI as a category of patients (i.e., PaO_2/FiO_2 201–300) that is separate from ARDS rather than an umbrella term for all patients (leading to the frequent use of the term ALI/ARDS that has no interpretation in the AECC definition). Under this new framework, each subcategory of ARDS (mild, moderate, severe) is defined by mutually exclusive ranges of PaO_2/FiO_2. The creation of the mild ARDS category formalizes what was previously perceived as patients with a less severe form of the syndrome but by applying the term ARDS, it recognizes the severity of their illness (mortality 27 % [22]) and response to lung protective ventilation

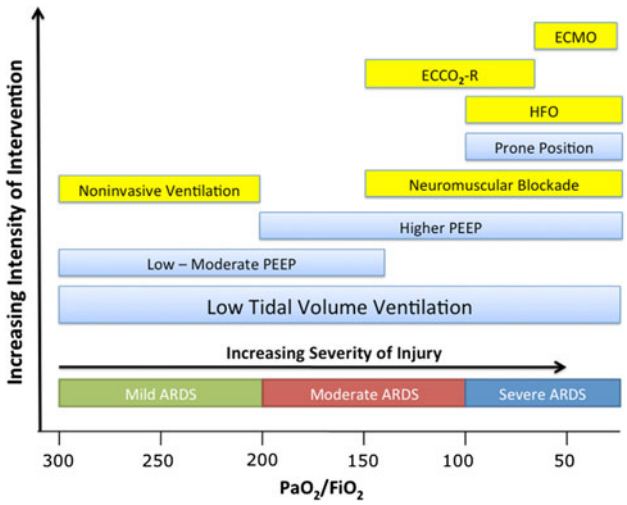

Fig. 1 Aligning Therapeutic Options with The Berlin Definition (adapted from [48] with permission). This figure depicts potential therapeutic options according to the severity of ARDS. Boxes in yellow represent therapies that in the opinion of the panel still require confirmation in prospective clinical trials. This figure is just a model based on currently available information. In the coming years, various aspects of the figure will likely change; proposed cut-offs may move, and some therapies may be found to not be useful, while others may be added

[29]. For severe ARDS, two possible thresholds were considered, $PaO_2/FiO_2 \leq 150$ or ≤ 100. The panel decided that the lower threshold may better represent the subgroup in which one could consider therapies that, in some studies appear to be beneficial in severe ARDS, such as prone positioning [30]. The committee felt that the new PaO_2/FiO_2 thresholds chosen for the different levels of ARDS severity could be helpful in categorizing patients with respect to different therapeutic approaches (Fig. 1).

Additional physiological measurements

Plateau pressure (as measured after an end-inspiratory pause) reflects the combined effects of tidal volume, PEEP, and the compliance of the respiratory system and is associated with mortality [31]. Theoretically, routine measurement of the plateau pressure may help in classifying patients based on their ARDS severity, aid in setting the ventilatory strategy, and in following the evolution of disease over time. However, plateau pressure is not routinely measured in some centers, and the use of certain ventilator modes (e.g., pressure-controlled ventilation) or supported ventilation with spontaneous breathing (e.g., pressure-support ventilation) render the measurement of plateau pressure impractical.

Static respiratory system compliance (i.e., the change in lung volume for a given driving pressure defined as tidal volume divided by plateau pressure minus PEEP) reflects the degree of lung volume loss. Although this measurement has the same concerns regarding feasibility as plateau pressure, the panel initially suggested including it (compliance <40 mL/cmH_2O) as part of the definition of Severe ARDS, based on a prior definition using a scoring system for ARDS [32]. Increased dead space is common in patients with ARDS and is associated with increased mortality [33, 34]. Measuring dead space, however, is challenging and was felt not to be feasible in routine clinical practice. As a rough surrogate of dead space, a minute ventilation corrected for $PaCO_2$ (calculated as minute ventilation × $PaCO_2$/40 mmHg) threshold of >10 L/min was initially chosen by the panel for the definition [35], as it corresponds approximately to a dead space fraction of 50 %, which was associated with increased mortality in a previous study [34]. However, static compliance and corrected minute ventilation were dropped from the final Berlin definition as they increased complexity without improving predictive validity. The panel was careful to emphasize, however, that the exclusion of these variables from the definition in no way decreases their importance in the daily evaluation and management of patients with ARDS.

Other criteria

We considered a number of additional potential diagnostic criteria for inclusion in the Berlin definition; a complete list of these and the reasons for their exclusion are shown in Table 4. Extravascular lung water (EVLW) can be measured using transpulmonary thermodilution techniques and high levels are associated with increased mortality in ARDS patients [36]. At the present time, technology to measure EVLW is relatively costly, invasive, not widely available, and has significant methodological limitations [37], so we did not include it in the definition. The panel also considered the potential inclusion of biomarkers (e.g., IL-6, TNF-α) or genetic markers (e.g., ACE gene polymorphism) to aid in the identification of patients with ARDS. Despite a large number of candidate biomarkers and genetic markers studied [38, 39], none has currently demonstrated adequate sensitivity and specificity for use in the diagnosis of ARDS [38–40].

Although the pathologic correlate of ARDS is diffuse alveolar damage (DAD), studies have demonstrated only moderate agreement between the clinical diagnosis of ARDS and DAD at autopsy [6]. Members of the panel were not in complete agreement that DAD is the sole pathologic correlate of ARDS, and some considered pneumonia and non-cardiogenic edema as compatible with ARDS when clinical criteria are met. Because of this, and since making a pathological diagnosis of ARDS using lung biopsy may be associated with increased risk of complications, the committee did not include this in the definition. At the present time, lung biopsy may be considered in patients with persistent ARDS of unknown etiology to rule out an underlying etiology that may respond to a specific treatment [41, 42].

Table 4 Criteria considered but not included in the Berlin definition (with permission from [21])

Category	Specific criterion	Rationale for inclusion	Reason not included
Oxygenation	Minimal FiO_2 requirement	More consistency to PaO_2/FiO_2 ratio [11]	Less feasible to mandate ventilator settings Less relevant for PaO_2/FiO_2 <100
	SpO_2/FiO_2 ratio	Improved feasibility [27]	Potential for misclassification of Mild as Severe ARDS [27]
	Higher PEEP requirement	More consistency to PaO_2/FiO_2 ratio [12, 13]	Less feasible to mandate ventilator settings
		Improved face validity for severe group	Does not improve predictive validity
Imaging	Thoracic computed tomography (CT)	Improved characterization of pulmonary opacities and lung volume [45]	Infeasible to mandate based on scanner availability and/or patient safety
	Opacities in 3–4 quadrants on frontal CXR	Improved face validity for severe group	Poor reliability of 2 vs. 3–4 quadrants [46]
		Associated with DAD [7]	Does not improve predictive validity
	Electrical impedance tomography	Improved characterization of pulmonary opacities and lung volume [47]	Infeasible to mandate based on availability Operating characteristics not well defined
Origin of edema	Extravascular lung water	Improved face validity Higher values associated with mortality [36]	Infeasible to mandate based on availability Does not distinguish hydrostatic vs. inflammatory pulmonary edema
	Inflammatory markers (IL-6 etc.)	Improved face validity [38]	Infeasible to mandate based on availability Operating characteristics poor [38, 40]
	Genetic markers	Improved face validity [39]	Infeasible to mandate based on availability Operating characteristics poor and lack of agreement on criterion standard [39]
Pulmonary mechanics	Plateau pressure	Improved face validity Higher values associated with mortality [31]	Less feasible to mandate ventilator settings
	Dead space	Improved face validity Higher values associated with mortality [34]	Infeasible to mandate based on availability
	Respiratory system compliance	Improved face validity	Does not improve predictive validity
	Minute ventilation	Improved face validity	Does not improve predictive validity
Pathology	DAD on lung biopsy	Confirmed pathological diagnosis [6, 42]	Infeasible to mandate lung biopsy

Continuous phenotype definition for ARDS

Previous investigators have hypothesized that differences in mortality rates reported in observational studies and variable responses to therapy in clinical trials may be due to arbitrary thresholds for hypoxemia in the definition, as well as variability in the interpretation of the other diagnostic criteria [43]. The panel considered the possibility of defining a continuous phenotype (e.g., probability and/or severity of ARDS defined with a numeric score) rather using a simple yes/no definition, which may better represent the clinical spectrum of ARDS [44]. Given the increase in complexity this would entail, along with uncertainty regarding the meaning and importance of an intermediate phenotype (e.g., meeting oxygenation criteria but with equivocal chest X-ray findings), the panel felt that further research was required before considering a continuous phenotype in the definition of ARDS.

The Berlin definition and future ARDS clinical trials

The panel recommends that future trials be designed using one or more of the ARDS subgroups as a base study population, which may be further refined using physiologic and/or other criteria specific to the putative mechanism of action of the study intervention (e.g., IL-6 levels for a trial of an IL-6 antagonist; more stringent hypoxemia criteria for a study on extracorporeal membrane oxygenation) (Fig. 1). The different categories of ARDS (mild, moderate, severe) may also be useful for stratification in clinical trials.

Future research on the Berlin ARDS definition

Some important first steps have already been taken in determining the frequency distribution of patients within

each subgroup of ARDS using this new definition [22]. Moreover, this work provides investigators with an idea of the proportion of patients in each risk category who may be eligible for inclusion in future clinical trials of therapeutic interventions and observational studies.

Implementation of the Berlin definition will over time allow for a formal evaluation of its feasibility (including barriers/facilitators to its uptake in clinical practice and research settings) and reliability of case identification based on each of the major diagnostic criteria (e.g., opacities on chest radiography, exclusion of hydrostatic pulmonary edema). The face and content validity of the Berlin definition may be assessed through feedback from a wider panel of clinicians and researchers. Finally, the criterion validity of the definition may be assessed by comparison to autopsy findings, both from pre-existing data and in future studies.

Ongoing research into the identification of accurate diagnostic and/or prognostic genetic polymorphisms or biomarkers for ARDS may help to further improve the specificity of the definition in the future. Similarly, reproducible and valid methods for the direct measurement of pulmonary vascular permeability or extravascular lung water will be important advances over current methods of assessing the presence and origin of lung edema, and could be incorporated into the future definition of ARDS.

Conclusions

The Berlin definition was developed to achieve a more reliable definition that will facilitate case recognition and better match treatment options and clinical outcomes to severity of illness categories. Important incremental advances in this ARDS definition include: the focus on feasibility, reliability, and validity during definition development; the incorporation of an empiric evaluation process in refining the definition [22]; and the creation of explicit examples to aid in application of the radiographic and origin of edema criteria (Online Supplement). The Berlin Definition will need to evolve as new information and experience is gained from its widespread implementation in clinical practice and research, as well as from the development of new diagnostic tools (e.g., imaging techniques, biomarkers, extravascular lung water measurement) which may be considered for inclusion in future ARDS definitions.

Acknowledgments We thank Salvatore Maggiore, MD, PhD (Department of Anesthesiology and Intensive Care, Agostino-Gemelli University Hospital, UniversitàCattolica del SacroCuore, Rome, Italy) and Anders Larsson, MD, PhD (Department of Surgical Sciences, Anesthesiology and Critical Care Medicine, Uppsala University, Uppsala, Sweden), for attending the round table as representatives of the European Society of Intensive Care Medicine. They received no compensation for their roles. We would like to thank Karen Pickett, MB BCh (Department of Intensive Care, Erasme Hospital, UniversitéLibre de Bruxelles, Brussels, Belgium), for her technical assistance in helping draft an earlier version of this manuscript. She received compensation for her role.

Conflicts of interest All authors have completed and submitted disclosure forms regarding their potential conflicts of interest. The meeting was convened and supported financially by the European Society of Intensive Care Medicine (ESICM). Dr. Ferguson is supported by a Canadian Institutes of Health Research New Investigator Award (Ottawa, Canada). Dr. Fan is supported by a Canadian Institutes of Health Research Fellowship Award (Ottawa, Canada). Dr. Rubenfeld is supported by the National Institutes of Health grant R01HL067939 (Bethesda, USA). None of the funding organizations or sponsors had any role in the design and conduct of the study; the collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Appendix

ARDS Task Force Members

Chairs

- V. Marco Ranieri, MD, PhD–Department of Anesthesia and Intensive Care Medicine, University of Turin, Turin, Italy
- Gordon D. Rubenfeld, MD, MSc–Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada
- B. Taylor Thompson, MD–Pulmonary/Critical Care Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA

Participants

- Antonelli, MD–Dipartimento di Anestesia e Rianimazione, Universita Cattolica del Sacro Cuore, Rome, Italy
- Antonio R. Anzueto, MD–Pulmonary/Critical Care, University of Texas Health Sciences Center at San Antonio, and South Texas Veterans Health Care System, San Antonio, TX
- Richard Beale, MBBS–Division of Asthma, Allergy and Lung Biology, King's College London and Department of Adult Critical Care, Guy's and St Thomas' NHS Foundation Trust, King's Health Partners, London–UK.
- Laurent Brochard, MD, PhD–Medical-Surgical Intensive Care Unit, Hopitaux Universitaires de Geneve, Geneva, Switzerland
- Roy G. Brower, MD–Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, MD
- Luigi Camporota, MD, PhD, MRCP–Division of Asthma, Allergy and Lung Biology, King's College London and Department of Adult Critical Care, Guy's

and St Thomas' NHS Foundation Trust, King's Health Partners, London–UK.
- Andrés Esteban MD, PhD–Servicio de Cuidados Intensivos, Hospital Universitario de Getafe. CIBER de Enfermedades Respiratorias, Instituto Salud Carlos III, Madrid, Spain
- Eddy Fan, MD–Interdepartmental Division of Critical Care Medicine, and Department of Medicine, University Health Network and Mount Sinai Hospital, University of Toronto, Toronto, Canada
- Niall D. Ferguson, MD, MSc–Interdepartmental Division of Critical Care Medicine, and Department of Medicine, Division of Respirology, University Health Network and Mount Sinai Hospital, University of Toronto, Toronto, Canada
- Luciano Gattinoni, MD–Istituto di Anestesiologia e Rianimazione, Universita degli Studi di Milano, Milan, Italy
- Andrew Rhodes, MD–Department of Intensive Care Medicine, St. George's Healthcare NHS Trust, London, England
- Arthur S. Slutsky, MD–Keenan Research Center of the Li KaShing Knowledge Institute of St. Michael's Hospital; Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada
- Jean-Louis Vincent, MD, PhD–Department of Intensive Care, Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium

References

1. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE (1967) Acute respiratory distress in adults. Lancet 2:319–323
2. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, LeGall JR, Morris A, Spragg R (1994) The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 149:818–824
3. Artigas A, Bernard GR, Carlet J, Dreyfuss D, Gattinoni L, Hudson L, Lamy M, Marini JJ, Matthay MA, Pinsky MR, Spragg R, Suter PM (1998) The American-European Consensus Conference on ARDS, part 2: ventilatory, pharmacologic, supportive therapy, study design strategies, and issues related to recovery and remodeling. Acute respiratory distress syndrome. Am J Respir Crit Care Med 157:1332–1347
4. Phua J, Badia JR, Adhikari NK, Friedrich JO, Fowler RA, Singh JM, Scales DC, Stather DR, Li A, Jones A, Gattas DJ, Hallett D, Tomlinson G, Stewart TE, Ferguson ND (2009) Has mortality from acute respiratory distress syndrome decreased over time?: a systematic review. Am J Respir Crit Care Med 179:220–227
5. Levy MM (2004) PEEP in ARDS–how much is enough? N Engl J Med 351:389–391
6. Esteban A, Fernández-Segoviano P, Frutos-Vivar F, Aramburu JA, Nájera L, Ferguson ND, Alía I, Gordo F, Ríos F (2004) Comparison of clinical criteria for the acute respiratory distress syndrome with autopsy findings. Ann Intern Med 141:440–445
7. Ferguson ND, Frutos-Vivar F, Esteban A, Fernández-Segoviano P, Aramburu JA, Nájera L, Stewart TE (2005) Acute respiratory distress syndrome: under recognition by clinicians and diagnostic accuracy of three clinical definitions. Crit Care Med 33:2228–2234
8. Kalhan R, Mikkelsen M, Dedhiya P, Christie J, Gaughan C, Lanken PN, Finkel B, Gallop R, Fuchs BD (2006) Underuse of lung protective ventilation: analysis of potential factors to explain physician behavior. Crit Care Med 34:300–306
9. Rubenfeld GD, Cooper C, Carter G, Thompson BT, Hudson LD (2004) Barriers to providing lung-protective ventilation to patients with acute lung injury. Crit Care Med 32:1289–1293
10. Villar J, Perez-Mendez L, Kacmarek RM (1999) Current definitions of acute lung injury and the acute respiratory distress syndrome do not reflect their true severity and outcome. Intensive Care Med 25:930–935
11. Gowda MS, Klocke RA (1997) Variability of indices of hypoxemia in adult respiratory distress syndrome. Crit Care Med 25:41–45
12. Ferguson ND, Kacmarek RM, Chiche J-D, Singh JM, Hallett DC, Mehta S, Stewart TE (2004) Screening of ARDS patients using standardized ventilator settings: influence on enrollment in a clinical trial. Intensive Care Med 30:1111–1116
13. Villar J, Perez-Mendez L, Lopez J, Belda J, Blanco J, Saralegui I, Suarez-Sipmann F, Lopez J, Lubillo S, Kacmarek RM (2007) An Early PEEP/FIO2 trial identifies different degrees of lung injury in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 176:795–804
14. Aboab J, Louis B, Jonson B, Brochard L (2006) Relation between PaO 2/FIO2 ratio and FIO2: a mathematical description. Intensive Care Med 32:1494–1497
15. Britos M, Smoot E, Liu KD, Thompson BT, Checkley W, Brower RG, National Institutes of Health Acute Respiratory Distress Syndrome Network Investigators (2011) The value of positive end-expiratory pressure and Fio_2 criteria in the definition of the acute respiratory distress syndrome. Crit Care Med 39:2025–2030
16. Rubenfeld GD, Caldwell E, Granton JT, Hudson LD, Matthay MA (1999) Interobserver variability in applying a radiographic definition for ARDS. Chest 116:1347–1353
17. Meade MO, Cook RJ, Guyatt GH, Groll RJ, Kachura JR, Bedard M, Cook DJ, Slutsky AS, Stewart TE (2000) Interobserver variation in interpreting chest radiographs for the diagnosis of acute respiratory distress syndrome. Am J Respir Crit Care Med 161:85–90
18. Ferguson ND, Meade MO, Hallett DC, Stewart TE (2002) High values of the pulmonary artery wedge pressure in patients with acute lung injury and acute respiratory distress syndrome. Intensive Care Med 28:1073–1077
19. National Heart Lung and Blood Institute Acute Respiratory Distress Syndrome ARDS Clinical Trials Network, Wheeler AP, Bernard GR, Thompson BT, Schoenfeld D, Wiedemann HP, deBoisblanc B, Connors AF, Hite RD, Harabin AL (2006) Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. N Engl J Med 354:2213–2224

20. Rubenfeld GD (2003) Epidemiology of acute lung injury. Crit Care Med 31(Supplement):S276–S284
21. ESCIM Congress Highlights (2011) ARDS: The "Berlin Definition". Available at: http://www.esicm.org/07-congresses/0A-annual-congress/webTv.asp. Accessed June 4, 2015
22. The ARDS Definition Task Force (2012) Acute respiratory distress syndrome: the Berlin definition. JAMA 307:2526–2533
23. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Muller NL, Remy J (2008) Fleischner Society: glossary of terms for thoracic imaging. Radiology 246:697–722
24. Katzenstein AL, Bloor CM, Leibow AA (1976) Diffuse alveolar damage—the role of oxygen, shock, and related factors. A review. Am J Pathol 85:209–228
25. Hudson LD, Milberg JA, Anardi D, Maunder RJ (1995) Clinical risks for development of the acute respiratory distress syndrome. Am J Respir Crit Care Med 151:293–301
26. Gajic O, Dabbagh O, Park PK, Adesanya A, Chang SY, Hou P, Anderson H 3rd, Hoth JJ, Mikkelsen ME, Gentile NT, Gong MN, Talmor D, Bajwa E, Watkins TR, Festic E, Yilmaz M, Iscimen R, Kaufman DA, Esper AM, Sadikot R, Douglas I, Sevransky J, Malinchoc M, U.S. Critical Illness and Injury Trials Group: Lung Injury Prevention Study Investigators (USCIITG-LIPS) (2011) Early identification of patients at risk of acute lung injury: evaluation of lung injury prediction score in a multicenter cohort study. Am J Respir Crit Care Med 183:462–470
27. Rice TW, Wheeler AP, Bernard GR, Hayden DL, Schoenfeld DA, Ware LB, for the National Institutes of Health, National Heart, Lung, and Blood Institute ARDS Network (2007) Comparison of the SpO_2/FIO_2 ratio and the PaO2/FIO2 ratio in patients with acute lung injury or ARDS. Chest 132:410–417
28. de Louw Van, Cracco C, Cerf C, Harf A, Duvaldestin P, Lemaire F, Brochard L (2001) Accuracy of pulse oximetry in the intensive care unit. Intensive Care Med 27:1606–1613
29. The Acute Respiratory Distress Syndrome Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301–1308
30. Sud S, Friedrich JO, Taccone P et al (2010) Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. Intensive Care Med 36:585–599
31. Hager DN, Krishnan JA, Hayden DL, Brower RG (2005) Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. Am J Respir Crit Care Med 172:1241–1245
32. Murray JF, Matthay MA, Luce JM, Flick MR (1988) An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 138:720–723
33. Gattinoni L, Vagginelli F, Carlesso E, Taccone P, Conte V, Chiumello D, Valenza F, Caironi P, Pesenti A, Prone-Supine Study Group (2003) Decrease in $PaCO_2$ with prone position is predictive of improved outcome in acute respiratory distress syndrome. Crit Care Med 31:2727–2733
34. Nuckton TJ, Alonso JA, Kallet RH, Daniel BM, Pittet J-F, Eisner MD, Matthay MA (2002) Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. N Engl J Med 346:1281–1286
35. Wexler HR, Lok P (1981) A simple formula for adjusting arterial carbon dioxide tension. Can Anaesth Soc J 28:370–372
36. Sakka SG, Rühl CC, Pfeiffer UJ, Beale R, McLuckie A, Reinhart K, Meier-Hellmann A (2000) Assessment of cardiac preload and extravascular lung water by single transpulmonary thermodilution. Intensive Care Med 26:180–187
37. Camporota L, De Neef M, Beale R (2012) Extravascular lung water in acute respiratory distress syndrome: potential clinical value, assumptions and limitations. Crit Care 16:114
38. Barnett N, Ware LB (2011) Biomarkers in acute lung injury—marking forward progress. Crit Care Clinics 27:661–683
39. Flores C, Pino-Yanes MM, Casula M, Villar J (2010) Genetics of acute lung injury: past, present and future. Minerva Anestesiol 76:860–864
40. Calfee CS, Ware LB, Glidden DV, Eisner MD, Parsons PE, Thompson BT, Matthay MA (2011) Use of risk reclassification with multiple biomarkers improves mortality prediction in acute lung injury. Crit Care Med 39:711–717
41. Papazian L, Doddoli C, Chetaille B, Gernez YL, Thirion X, Roch A, Donati Y, Bonnety M, Zandotti C, Thomas P (2007) A contributive result of open-lung biopsy improves survival in acute respiratory distress syndrome patients. Crit Care Med 35:755–762
42. Papazian L, Thomas P, Bregeon F, Garbe L, Zandotti C, Saux P, Gaillat F, Drancourt M, Auffray JP, Gouin F (1998) Open-lung biopsy in patients with acute respiratory distress syndrome. Anesthesiology 88:935–944
43. Kraus PA, Lipman J, Lee CC, Wilson WE, Scribante J, Barr J, Mathivha LR, Brown JM (1993) Acute lung injury at Baragwanath ICU. An eight-month audit and call for consensus for other organ failure in the adult respiratory distress syndrome. Chest 103:1832–1836
44. Shah CV, Lanken PN, Localio AR, Gallop R, Bellamy S, Ma SF, Flores C, Kahn JM, Finkel B, Fuchs BD, Garcia JG, Christie JD (2010) An alternative method of acute lung injury classification for use in observational studies. Chest 138:1054–1061
45. Gattinoni L, Caironi P, Pelosi P, Goodman LR (2001) What has computed tomography taught us about the acute respiratory distress syndrome? Am J Respir Crit Care Med 164:1701–1711
46. Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, Stern EJ, Hudson LD (2005) Incidence and outcomes of acute lung injury. N Engl J Med 353:1685–1693
47. Zhao Z, Steinmann D, Frerichs I, Guttmann J, Möller K (2010) PEEP titration guided by ventilation homogeneity: a feasibility study using electrical impedance tomography. Crit Care 14:R8
48. Froese AB, Ferguson ND (2012) High-Frequency Ventilation. In: Tobin MJ (ed) Mechanical Ventilation (3rd edn). McGraw-Hill, New York, In Press